Organic Syntheses

(*R*)-2,2,2-Trichloro-1-phenylethyl (methylsulfonyl)-oxycarbamate

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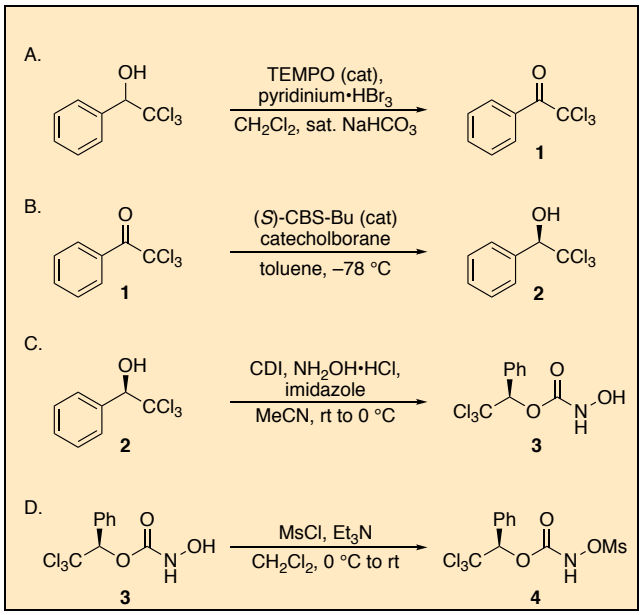

Procedure (Note 1)

A. *2,2,2-Trichloro-1-phenylethan-1-one* (***1***). A 2000-mL Erlenmeyer-flask equipped with a 7 cm flat magnetic stirrer is charged with (±)-2,2,2-trichloro-1-phenylethan-1-ol (38.3 g, 170 mmol, 1.00 equiv) (Note 2), dichloromethane (350 mL) (Note 3) and saturated $NaHCO_3$ (700 mL) (Note 4). The solution is stirred vigorously (900 rpm). To this solution is added

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TEMPO (2.66 g, 17.0 mmol, 0.10 equiv) (Note 5) at 23 °C. The resulting orange/red solution is cooled to 0 °C (Note 6) and pyridinium tribromide (81.6 g, 255 mmol, 1.50 equiv) (Note 7) is carefully added portion wise (Note 8) (Figure 1A). After the addition is complete, the solution is allowed to warm to 23 °C and stirred vigorously for 2 h (Note 9). After completion, the red solution is cooled to 0 °C and excess oxidant quenched by addition of 5% $Na_2S_2O_3$ solution (250 mL) (Notes 10 and 11) (Figure 1B).

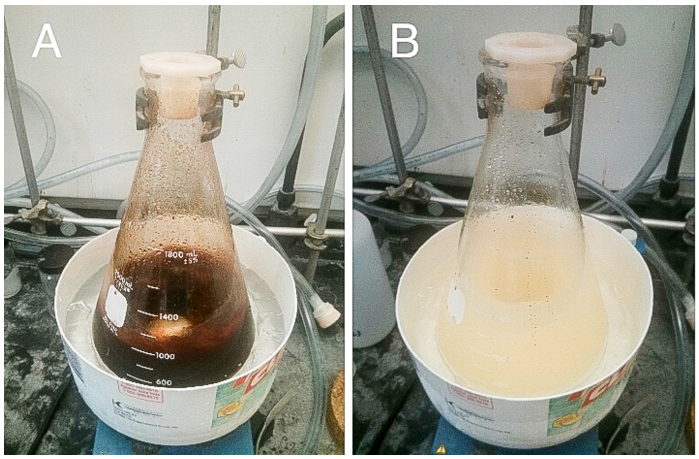

Figure 1A. Reaction set-up; 1B. After quench
(Photos provided by submitters)

The magnetic stir bar is removed and the solution is poured in a 2000-mL separatory funnel. The layers are separated and the aqueous layer is extracted with dichloromethane (2 x 200 mL) and EtOAc (2 x 200 mL). The combined organic layers are dried over $MgSO_4$ (30 g), filtered through an 8 cm diameter fritted glass funnel into a 2000-mL round bottomed flask, washed with EtOAc (75 mL) (Note 12) and concentrated using a rotary evaporator (38 °C, 375 mmHg to 35 mmHg) (Notes 13 and 14). The crude material is purified by flash chromatography using hexanes as eluent (200 g silica gel, eluent: hexanes, dimension: 14.0×6.5 cm, fraction size: 50 mL) to afford the pure product as a slightly yellow liquid (28.5 g, 75% yield) (Notes 15, 16, 17, and 18).

B. *(R)-2,2,2-Trichloro-1-phenylethan-1-ol* (**2**). A 1000-mL three-necked round-bottomed flask equipped with a 4 cm egg-shaped magnetic stirred is flame-dried under argon, then charged, after cooling back to 23 °C, with **1**

(27.9 g, 125 mmol, 1.00 equiv) dissolved in dry toluene (320 mL) (Note 19). (*S*)-(−)-2-Butyl-CBS-oxazaborolidine ((*S*)-CBS-Bu catalyst) in toluene (1.00 M, 6.25 mL, 6.25 mmol, 5.0 mol %) (Notes 20, 21, and 22) is added via a cannula to the reaction mixture and the resulting mixture is cooled to –78 °C (Note 23). A 1.05 M solution of catecholborane in THF (190 mL, 190 mmol, 1.60 equiv) (Note 24) is then carefully added dropwise over 7–9 h using a 500 mL dried pressure-equalized addition funnel to the stirred reaction mixture (500–600 rpm) (Note 25) (Figure 2).

Figure 2. Reaction set-up (Photo provided by submitters)

After 12 h of reaction (including the addition time), the solution is allowed to slowly warm to 23 °C (Note 26) and stirred at room temperature for 16 h. The solution is cooled to 0 °C (Note 6) and quenched by slow addition of water (230 mL) (Note 27) followed by EtOAc (230 mL). The biphasic mixture is poured in a 2000-mL separatory funnel and the layers are separated. The aqueous layer is extracted with EtOAc (140 mL) and the combined organic layers are washed with 2 M NaOH solution (5 x 180 mL) (Note 28) (Figure 3), 1 M HCl solution (3 x 140 mL) and saturated NaCl solution (140 mL). The organic layer is then dried over $MgSO_4$ (~20 g), filtered through a 4 cm diameter fritted glass funnel, washed with EtOAc (50 mL) and concentrated under reduced pressure (35–40 °C, 150 to 15 mmHg). The crude (yellow oily liquid) is then purified by filtration through a short pad of silica gel (135 g, eluent: Et_2O:hexanes (1:9), dimension: 13.0×6.0 cm, fraction size: 50 mL for the first eight fractions, then 150 mL for the next eight fractions) (Note 29). The fractions containing the product are collected in a 2000-mL round-bottomed flask and evaporated (225 to 15 mmHg, 40 °C). The resulting liquid is then dried *in vacuo* to afford

the pure chiral alcohol as a colorless liquid (28.0 g, 99% yield, 94% ee) (Notes 30 and 31).

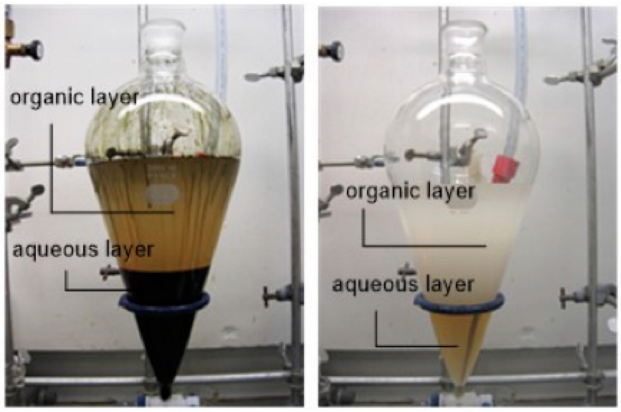

Figure 3. After the first and the last basic wash (Photos provided by submitters)

C. *(R)-2,2,2-Trichloro-1-phenylethyl hydroxycarbamate* (**3**). A 1000-mL two-necked round-bottomed flask equipped with a 4 cm egg-shaped magnetic stirrer is flame-dried under argon atmosphere, then charged, after cooling back to room temperature, with **2** (27.3 g, 121 mmol, 1.00 equiv) and dry acetonitrile (300 mL) (Note 32). 1,1′-Carbonyldiimidazole (CDI) (21.6 g, 133 mmol, 1.10 equiv) (Note 33) is then added portion wise (Note 34) to the stirred solution (400–500 rpm) (Note 35) (Figure 4).

Figure 4. Reaction set-up (Photo provided by submitters)

The resulting mixture is stirred at 23 °C for 2 h or until the reaction reached completion (Note 36). The solution is then cooled to 0–5 °C (Note 5) before hydroxylamine hydrochloride (33.6 g, 484 mmol, 4.00 equiv) (Note 37 and 38) and imidazole (24.7 g, 363 mmol, 3.00 equiv) (Note 39) are successively added to the heterogeneous solution (Note 40). The resulting mixture is stirred at 0–5 °C for 45 min (Note 41). After the reaction is complete, acetonitrile is removed by evaporation under reduced pressure (180 to 15 mmHg, 40 °C). The residue is dissolved in a (5:1) mixture of 10% w/w HCl solution and EtOAc (450 mL total volume: 375 mL 10% w/w HCl and 75 mL EtOAc). The biphasic mixture is poured in a 1000-mL separatory funnel and the layers are separated. The aqueous layer is extracted with EtOAc (2 x 100 mL). The combined organic layers are washed with a saturated NaCl solution (200 mL), dried over Na_2SO_4 (20 g), filtered, washed with EtOAc (50 mL) and concentrated (35–40 °C, 150 to 15 mmHg) (Note 42). The resulting pale yellow oil is purified by precipitation in hexanes: the crude *N*-hydroxycarbamate is dissolved in chloroform (10 mL) (Note 43), and the resulting solution is added dropwise to hexanes (1000 mL) (Note 15) that is vigorously stirred (700 rpm) in a 2000-mL Erlenmeyer-flask with an 8 cm magnetic stir bar. A white solid is formed during addition. The solid is then collected by filtration through a 4 cm diameter fritted glass funnel, washed with hexanes (75 mL) and dried *in vacuo* to afford the desired product as a colorless solid (29.5 g, 86% yield) (Notes 44, 45, 46, and 47).

D. *(R)-2,2,2-Trichloro-1-phenylethyl (methylsulfonyl)oxycarbamate (**4**).* A 250-mL round-bottomed flask equipped with a 3 cm egg-shaped magnetic stirrer is flame-dried under argon atmosphere, then charged, after cooling back to 23 °C, with **3** (4.20 g, 13.8 mmol, 1.15 equiv) and dry dichloromethane (30 mL) (Note 48). The solution is stirred at 0 °C (500 rpm) and triethylamine (1.67 mL, 12.0 mmol, 1.00 equiv) is added to the solution with a syringe (Note 49). Methanesulfonyl chloride (933 μL, 12.0 mmol, 1.00 equiv) (Note 50) is then added dropwise (over 5 min) to the mixture at 0 °C. The resulting mixture is then stirred at 23 °C for 1 h (Note 51). After the reaction is complete, the reaction is quenched by addition of water (20 mL). The biphasic mixture is poured in a 250-mL separatory funnel and the layers are separated. The organic layer is washed with water (25 mL) and re-extracted with dichloromethane (5 mL). The combined organic layers are washed with brine (25 mL) (Note 52), dried over Na_2SO_4 (~8 g), filtered through cotton, washed with dichloromethane (10 mL), and concentrated under reduced pressure (325 to 15 mmHg at 40 °C) to afford a pale yellow

sticky oil. The crude material is purified by flash chromatography (470 g silica gel, eluent: Et_2O:pentane (1:4), dimension: 28.0 × 6.5 cm, fraction size: 1600 mL for the first three fractions, then 80 mL for the next eighty fractions) (Notes 53 and 54). A total of 2.87–3.27 g (66–75% yield) of the desired product is obtained as a pure colorless solid (Notes 55, 56, and 57).

Notes

1. Prior to performing each reaction, a thorough hazard analysis and risk assessment should be carried out with regard to each chemical substance and experimental operation on the scale planned and in the context of the laboratory where the procedures will be carried out. Guidelines for carrying out risk assessments and for analyzing the hazards associated with chemicals can be found in references such as Chapter 4 of "Prudent Practices in the Laboratory" (The National Academies Press, Washington, D.C., 2011; the full text can be accessed free of charge at https://www.nap.edu/catalog/12654/prudent-practices-in-the-laboratory-handling-and-management-of-chemical. See also "Identifying and Evaluating Hazards in Research Laboratories" (American Chemical Society, 2015) which is available via the associated website "Hazard Assessment in Research Laboratories" at https://www.acs.org/content/acs/en/about/governance/committees/chemicalsafety/hazard-assessment.html. In the case of this procedure, the risk assessment should include (but not necessarily be limited to) an evaluation of the potential hazards associated with (±)-2,2,2-trichloro-1-phenylethan-1-ol, sodium bicarbonate, dichloromethane, sodium thiosulfate, TEMPO, pyridinium tribromide, ethyl acetate, magnesium sulfate, hexanes, silica gel, toluene, (*S*)-CBS-Bu, catecholborane, tetrahydrofuran, sodium hydroxide, hydrochloric acid, sodium chloride, diethyl ether, acetonitrile, 1,1'-carbonyldiimidazole, hydroxylamine hydrochloride, imidazole, sodium sulfate, chloroform, triethylamine, and methanesulfonyl chloride.
2. (±)-2,2,2-Trichloro-1-phenylethan-1-ol is prepared using the procedure described in *Org. Synth.* **1968**, *48*, 27–29. The submitters prepared and provided the sample of (±)-2,2,2-trichloro-1-phenylethan-1-ol (~98% purity) used for checking. (±)-2,2,2-Trichloro-1-phenylethan-1-ol is also commercially available.

3. Dichloromethane (certified ACS) is purchased from Caledon Company and used as received.
4. Sodium bicarbonate is purchased from Caledon Company and used as received. The saturated solution is prepared by adding 90 g of sodium bicarbonate to 1000 mL of distilled water.
5. TEMPO is purchased from Sigma-Aldrich Fine Chemicals Company Inc.
6. An ice/water bath is used.
7. Pyridinium tribromide (90% grade) is purchased from Sigma-Aldrich Fine Chemicals Company Inc and is used as received.
8. Portions of 5-10 g are added every 2 minutes, for a total addition of 15–20 minutes (a foam can form if the addition is too fast). The solution must be vigorously stirred (900 rpm or more).
9. The reaction is monitored by TLC analysis on silica gel using a mixture of Et_2O:hexanes (1:9) and visualization with UV light and $KMnO_4$ (R_f of starting material = 0.16, R_f of product = 0.68).
10. Sodium thiosulfate is purchased from Merck KGaA. The 5% w/w solution is prepared by dissolving 78 g of sodium thiosulfate pentahydrate ($Na_2S_2O_3 \cdot 5H_2O$) in 1000 mL of distilled water.
11. The red solution becomes yellow upon the addition of sodium thiosulfate.
12. A TLC analysis is performed on the last drop of filtration to be sure that all the product has been collected.
13. The checkers recommend the concentration of the crude on a rotary evaporator in a fume hood due to the presence of pyridine.
14. Submitters suggested purification by distillation using the following conditions: The crude material is suspended in hexanes (200 mL) (Note 15) and silica gel (30 g) (Note 16) is added to trap the colored impurities. The mixture is filtered through a pad of silica gel (15 g), washed with hexanes (600 mL) and the filtrate is evaporated *in vacuo* (38 °C, 375 to 35 mmHg). The resulting pale yellow liquid is distilled under reduced pressure (oil-bath: 80 °C to 120 °C, 0.2 mmHg, main fraction: bp 55–64 °C at 0.2 mmHg). The distillation short path is equipped with a 15 cm Vigreux column and grease is used for all joints. Checkers found that purification by distillation as described did not reliably provide the highest purity product (Note 17).
15. Hexanes (certified ACS) is purchased from Fisher Scientific Company and used as received.

16. Silica gel F60 type, 40-63 μm (230-400 mesh) is purchased from Zeochem AG Inc.
17. The checkers found that an additional purification by flash chromatography was necessary after distillation to obtain analytically pure product.
18. A second reaction performed on half-scale provided 15.0 g (79%) of the same product, after purification by distillation and chromatography. Analytical data for 2,2,2-trichloro-1-phenylethan-1-one (**1**). R_f = 0.66–0.69 (Et_2O:hexanes (1:9)); ^1H NMR (400 MHz, $CDCl_3$) δ: 7.48–7.53 (m, 2H), 7.62–7.66 (m, 1H), 8.25–8.28 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 95.6, 128.5, 129.2, 131.6, 134.4, 181.4; IR (film, ATR-FTIR) 1709, 1596, 1448, 1221, 1005, 820, 650 cm^{-1}; HRMS (ESI+) calc. for $C_8H_6Cl_3O$ $[M+H]^+$: 222.9479; found: no exact mass found by ESI+; Anal. calc. for $C_8H_5Cl_3O$: C, 43.00, H, 2.26; found: C, 43.21, H, 2.19.
19. Dry toluene from a column purification solvent system (using activated alumina and CuO (treated with H_2) columns) under argon atmosphere is employed.
20. (*S*)-CBS-Bu catalyst (1.00 M in toluene) is purchased from Sigma-Aldrich Fine Chemicals Company Inc.
21. The checkers used commercially available solution of catalyst (Note 20). The submitters prepared a solution of (*S*)-CBS-Bu according to the following procedure: A 100 mL round-bottomed flask, equipped with a magnetic stirrer, is charged with *n*–butylboronic acid (780 mg, 7.70 mmol, 1.10 equiv), (*S*)–diphenyl-prolinol (1.77 g, 7.00 mmol, 1.00 equiv) and toluene (35 mL). The flask is then equipped with a Dean-Stark apparatus filled with toluene, put under argon, stirred and heated to reflux overnight. The solution is then used directly in the reaction without any purification.
22. Checkers found that the reaction with commercially available (*S*)-CBS-Bu catalyst (1.00 M in toluene) proceeded with the same efficiency, with respect to yield and level of enantioselection, as described by the submitters.
23. A dry ice/acetone bath is used. A period of 20–30 min is typically needed to reach –78 °C inside the reaction mixture.
24. A 1 M solution of catecholborane in THF (1.05 M according to the specification sheet) is purchased from Sigma-Aldrich Fine Chemicals Company Inc.

25. An internal thermostat probe is used to monitor the temperature of the solution. Addition rate (one drop every 5 seconds approximately) is carefully controlled to maintain the temperature below –65 °C.
26. The dry ice/acetone bath should not be removed during the warming to allow a slow increase of the temperature of the solution mixture. The checkers note that the warming of the solution to room temperature as described in this note by the submitters took 24–36 h.
27. Water is added dropwise (two drops per second) as rapid evolution of H_2 is observed.
28. The aqueous layer becomes green/black during the washing. The aqueous washings are performed until the aqueous layer becomes light brown. The checkers observed that the basic wash slightly warmed and slow phase separation was noted in the 4th and 5th wash.
29. Approx. 2000 mL of eluent is required.
30. The checkers noted a slightly higher level of enantioselection on half-scale experiment (14.5 g, 65.0 mmol of **1**), which afforded 14.6 g of alcohol **2** as colorless liquid (>99% yield, 96% ee).
31. Analytical data for (*R*)-2,2,2-trichloro-1-phenylethan-1-ol (**2**). R_f = 0.24–0.27 (Et_2O:hexanes (2:8)); ^1H NMR (400 MHz, $CDCl_3$) δ: 3.41 (d, *J* = 4.0 Hz, 1H), 5.21 (d, *J* = 3.9 Hz, 1H), 7.38–7.45 (m, 3H), 7.62–7.65 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 84.6, 103.2, 127.9, 129.3, 129.6, 134.9; IR (film, ATR-FTIR) 3450, 1454, 1059, 817, 743 cm^{-1}; $[\alpha]_D^{24}$ –39.2 (c 1.00, $CHCl_3$); Enantiomeric ratio is determined to be 97.1:2.9 by analytical HPLC, using the following conditions: Chiracel-OD chiralpak column (4.6 mm x 250 mm, particle size 10 μm, part #14025); 10% isopropanol in hexanes for 30 min, flow 1.0 mL/min, 210 nm detection; retention time: t_{major} = 8.5 min and t_{minor} = 11.4 min; HRMS (ESI+) calc. for $C_8H_7Cl_3NaO$ $[M+Na]^+$: 246.9455; found: no exact mass found by ESI+; Anal. Calcd for $C_8H_7Cl_3O$: C, 42.61, H, 3.13, found: C, 42.99, H, 3.05.
32. Dry acetonitrile from a solvent purification system (using two neutral activated alumina columns) under argon atmosphere is employed.
33. 1,1′-Carbonyldiimidazole is purchased from Alfa Aesar and stored in glovebox prior to use.
34. Portions of 5 g are added every minute.
35. The solution becomes heterogeneous over time. A white precipitate appears a few minutes after the addition of CDI.
36. The reaction is monitored by TLC analysis on silica gel using EtOAc:hexanes (2:8) and visualization with UV light and $KMnO_4$ (R_f of starting material = 0.5, R_f of intermediate = 0.2).

37. The hydroxylamine hydrochloride salt is purchased from Sigma-Aldrich Fine Chemicals Company Inc.
38. Hydroxylamine hydrochloride is hygroscopic and is dried in an oven (110 °C) overnight before use.
39. Imidazole (99% grade) is purchased from Alfa Aesar and used as received.
40. The precipitate disappears for a while before another beige precipitate appears after the addition.
41. The reaction is monitored by TLC analysis on silica gel using EtOAc in hexanes (3:7) and visualization with UV light and $KMnO_4$ (R_f of product = 0.34).
42. Checkers observed some solid formation in the crude material.
43. Chloroform is purchased from Fisher Chemicals and used as received.
44. Checkers found that upon concentration of the mother liquor to approx. 100 mL, additional product precipitates. This second crop of product is an equal mixture of product **3** and starting material **2** and can give another ~1 g of the product **3** upon purification by flash chromatography (Note 46).
45. Checkers noted formation of product **3** with similar efficiency and with the similar purity for first and second crops on half-scale experiment (13.5 g, 60.0 mmol of **2**), affording 14.8 g of product **3** as colorless solid (87%) in first crop.
46. Analytical data for (*R*)-2,2,2-trichloro-1-phenylethyl hydroxycarbamate (**3**). R_f = 0.34-0.37 (EtOAc:hexanes (3:7)); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.30 (s, 1H), 6.88 (br, 1H), 7.36-7.45 (m, 3H), 7.56-7.59 (m, 3H) (OH under this band); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 84.2, 99.1, 128.1, 129.7, 130.1, 132.6, 156.8; IR (solid, ATR-FTIR) 3326, 1743, 1453, 1245, 1118, 751 cm^{-1}; mp 93–96 °C (checkers note the mp for purified product is 97-100 °C); $[\alpha]_D^{25}$ –35.8 (c 1.00, $CHCl_3$); HRMS (ESI+) calc. for $C_9H_8Cl_3NNaO_3$ $[M+Na]^+$: 305.9462; found: 305.9464; Anal. calc. for $C_9H_8Cl_3NO_3$: N, 4.92, C, 37.99, H, 2.83; found: N, 4.81, C, 37.99, H, 2.71. (A sample is purified by flash chromatography eluting with MeOH in DCM (3:97) before performing the elemental analysis. NMR spectra of both, the product before and after purification are provided. The crude product (93.5% w/w) is directly used for subsequent reaction.).
47. Consistent with the submitters observations, the checkers observed no difference in use of product **3** directly from first crop or after chromatographic purification (Note 46). Checkers found that the purity of the isolated product in the first crop is 92.0% n/n, 93.5% w/w,

exactly the same as provided by submitters. The product **3** is isolated along with remaining starting alcohol **2**.

48. Dry DCM from a column purification solvent system (using two neutral activated alumina columns) under argon atmosphere is employed.
49. Anhydrous triethylamine from a solvent purification system (using two neutral activated alumina columns) under argon atmosphere is employed.
50. Methanesulfonyl chloride is purchased from Sigma-Aldrich Fine Chemicals Company Inc. and is freshly distilled under vacuum over P_2O_5 prior to use.
51. The reaction is monitored by TLC analysis on silica gel using EtOAc:hexanes (1:2) and visualization with UV light and $KMnO_4$ (R_f of product = 0.47).
52. Shaking too violently will produce an emulsion.
53. The checkers isolated analytically pure product **4** reliably by flash column chromatography, and careful analysis of the fractions prior to collection. Due to close elution of a byproduct (^{1}H NMR resonance at 6.28 ppm) with product **4**, fractions containing product were subject to ^{1}H NMR analysis in addition to TLC analysis. Only fractions with >99% purity of product are combined, concentrated, and dried *in vacuo*. Any mixed fractions are combined, concentrated, and re-purified by a second flash column chromatography using the same eluent with the 100-fold mass of silica gel compared to the mass of the mixed fraction. Checkers recommend a height-to-diameter ratio of the column between 6-8 for the second flash chromatography.
54. While the submitters described purification of **4** by crystallization, after significant experimentation the checkers were not able to confirm this method as a reliable means for purification of **4**. Thus, the checkers used flash chromatography conditions based on those described in Lebel, H.; Piras, H; Bartholoméüs, J *Angew. Chem. Int. Ed.* **2014**, *53*, 7300–7304.
55. Checkers found that concentration of the pure product from dichloromethane is necessary to remove trace amounts of Et_2O. The sample is dried *in vacuo* in a 500-mL round-bottomed flask for 48 h to afford solvent-free product **4**.
56. Checkers noted that the purification of compound **3** had no impact on success of reaction step D, consistent with the submitters' observations. Checkers performed reaction step D on ~1 g scale with both crude (first crop, 92% purity) and purified compound **3** (Note 46) and observed

similar yields, and overall outcome consistent with results described here for the multi-gram scale.

57. Analytical data for (*R*)-2,2,2-trichloro-1-phenylethyl (methylsulfonyl)-oxycarbamate (**4**): R_f = 0.47–0.50 (EtOAc:hexanes (3:7)); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.20 (s, 3H), 6.35 (s, 1H), 7.40-7.49 (m, 3H), 7.60-7.63 (m, 2H), 8.46 (s (br), 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 36.7, 85.2, 98.6, 128.4, 129.7, 130.5, 131.7, 153.8; IR (solid, ATR-FTIR) 3276, 2940, 1753, 1455, 1374, 1234, 1182, 1092, 969, 787, 699 (cm^{-1}); mp = 75–81 °C; $[\alpha]_D^{24}$ –15.9 (c 1.47, $CHCl_3$); HMRS (ESI+) calc. for $C_{10}H_{10}Cl_3NNaO_5S$ [M+Na]+: 383.9259; found: 383.9240; Anal. calc. for $C_{10}H_{10}Cl_3NO_5S$: N, 3.86, C, 33.12, H, 2.78, S, 8.84; found: N, 3.91, C, 33.38, H, 2.74, S, 8.87.

Working with Hazardous Chemicals

The procedures in *Organic Syntheses* are intended for use only by persons with proper training in experimental organic chemistry. All hazardous materials should be handled using the standard procedures for work with chemicals described in references such as "Prudent Practices in the Laboratory" (The National Academies Press, Washington, D.C., 2011; the full text can be accessed free of charge at http://www.nap.edu/catalog.php?record_id=12654). All chemical waste should be disposed of in accordance with local regulations. For general guidelines for the management of chemical waste, see Chapter 8 of Prudent Practices.

In some articles in *Organic Syntheses*, chemical-specific hazards are highlighted in red "Caution Notes" within a procedure. It is important to recognize that the absence of a caution note does not imply that no significant hazards are associated with the chemicals involved in that procedure. Prior to performing a reaction, a thorough risk assessment should be carried out that includes a review of the potential hazards associated with each chemical and experimental operation on the scale that is planned for the procedure. Guidelines for carrying out a risk assessment and for analyzing the hazards associated with chemicals can be found in Chapter 4 of Prudent Practices.

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Discussion

N-Sulfonyloxycarbamates are electrophilic nitrogen reagents that are used in numerous reactions involving the formation of C-N bonds.[2,3,4,5,6,7,8,9,10,11] These reagents have emerged as alternative metal nitrene precursors, namely to perform aziridination and C-H amination reactions.[12,13,14,15,16,17] Among these reagents, (*R*)-2,2,2-trichloro-1-phenylethyl (methylsulfonyl)oxycarbamate is reported to undergo stereoselective C-H amination,[18] thioether amination[19,20] and aziridination reactions,[21] in the presence of $Rh_2\{(S)\text{-4-Br-nttl}\}_4$ or $Rh_2\{(S)\text{-nttl}\}_4$.

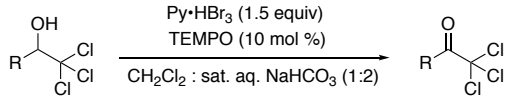
The chiral alcohol ((*R*)-2,2,2-trichloro-1-phenylethan-1-ol) is prepared via the Corey CBS reduction of the corresponding ketone.[22,23] It should be noted that the facial selectivity is inverted in comparison with the result obtained for the asymmetric CBS reduction of acetophenone. Other enantioselective reduction methods failed to afford the desired alcohol with high enantiomeric excess. [24,25,26,27]

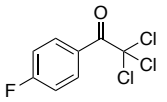
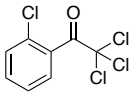
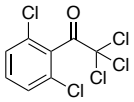
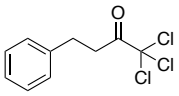
2,2,2-Trichloroacetophenone is not commercially available, but is accessible via the oxidation of racemic 2,2,2-trichloro-1-phenylethan-1-ol. At the outset, a mixture of sodium dichromate, sulfuric acid in glacial acetic was used, as reported in the literature.[28] Recently a novel procedure to oxidize highly electrophilic halogenated ketones was reported, using a mixture of pyridinium tribromide and catalytic amount of a modified TEMPO.[29] This procedure has been adapted for the standard TEMPO reagent and is now used to prepare 2,2,2-trichloroacetophenone in high yields and under more environmentally friendly reaction conditions (compared to chromium (VI) oxidation reaction conditions). The procedure could also be used to oxidize other aryl trichloroethanol derivatives (Table 1, entries 1–3). Aliphatic trichloroethanol derivatives were less reactive and only low yields were obtained, even under refluxing reaction conditions for a longer period of time (entry 4).

The *N*-mesyloxycarbamate reagent is prepared in two steps from (*R*)-2,2,2-trichloro-1-phenylethan-1-ol via the corresponding *N*-hydroxy-carbamate. Both products are solids and can be purified by flash column

chromatography. (*R*)-2,2,2-trichloro-1-phenylethyl (methylsulfonyl)oxycarbamate is highly stable (DSC/TGA analysis shows decomposition starting at 180 °C) and can be kept on the bench for an unlimited amount of time. The *N*-mesyloxycarbamate reagent is highly hygroscopic and up to 1 equiv of water may be associated with the reagent, as shown in the reported X-ray crystal structure.[18] The described procedure can be used to prepared a number of *N*-mesyloxycarbamates derived from primary and secondary alcohols.[30]

Table 1. Synthesis of various trichloroacetophenones



entry	conditions	product	yield (%)
1	25 °C, 12 h		75
2	25 °C, 4 h		91
3	25 °C, 4 h		87
4	45 °C, 14 h		28

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Appendix
Chemical Abstracts Nomenclature (Registry Number)

2,2,2-Trichloro-1-phenylethan-1-one; 2,2,2-Trichloroacetophenone:
Ethanone, 2,2,2-trichloro-1-phenyl-; (2902-69-4)
(±)-2,2,2-Trichloro-1-phenylethan-1-ol: Benzenemethanol,
α-(trichloromethyl)-; (2000-43-3)
(*R*)-2,2,2-Trichloro-1-phenylethan-1-ol: Benzenemethanol,
α-(trichloromethyl)-, (α*R*)-; (53432-39-6)
TEMPO: 1-Piperidinyloxy, 2,2,6,6-tetramethyl-; (2564-83-2)
Pyridinium tribromide: Hydrogen tribromide, compd. with pyridine (1:1);
(39416-48-3)
n-Butylboronic acid: Boronic acid, *B*-butyl-; (4426-47-5)
(*S*)-Diphenylprolinol: 2-Pyrrolidinemethanol, α,α-diphenyl-, (2*S*)-;
(112068-01-6)
Catecholborane: 1,3,2-Benzodioxaborole; (274-07-7)
(*R*)-2,2,2-Trichloro-1-phenylethyl hydroxycarbamate: Carbamic acid, *N*-
hydroxy-, (1*R*)-2,2,2-trichloro-1-phenylethyl ester; (1391854-32-2)
1,1′-Carbonyldiimidazole (CDI): Methanone, di-1*H*-imidazol-1-yl-;
(530-62-1)
Hydroxylamine hydrochloride: Hydroxylamine, hydrochloride (1:1);
(5470-11-1)
(*R*)-2,2,2-Trichloro-1-phenylethyl (methylsulfonyl)oxycarbamate:
Methanesulfonic acid, [[(1*R*)-2,2,2-trichloro-1-phenylethoxy]carbonyl]azanyl
ester; (1391853-96-5)
Triethylamine: Ethanamine, *N*,*N*-diethyl-; (121-44-8)
Mesyl chloride: Methanesulfonyl chloride; (124-63-0)

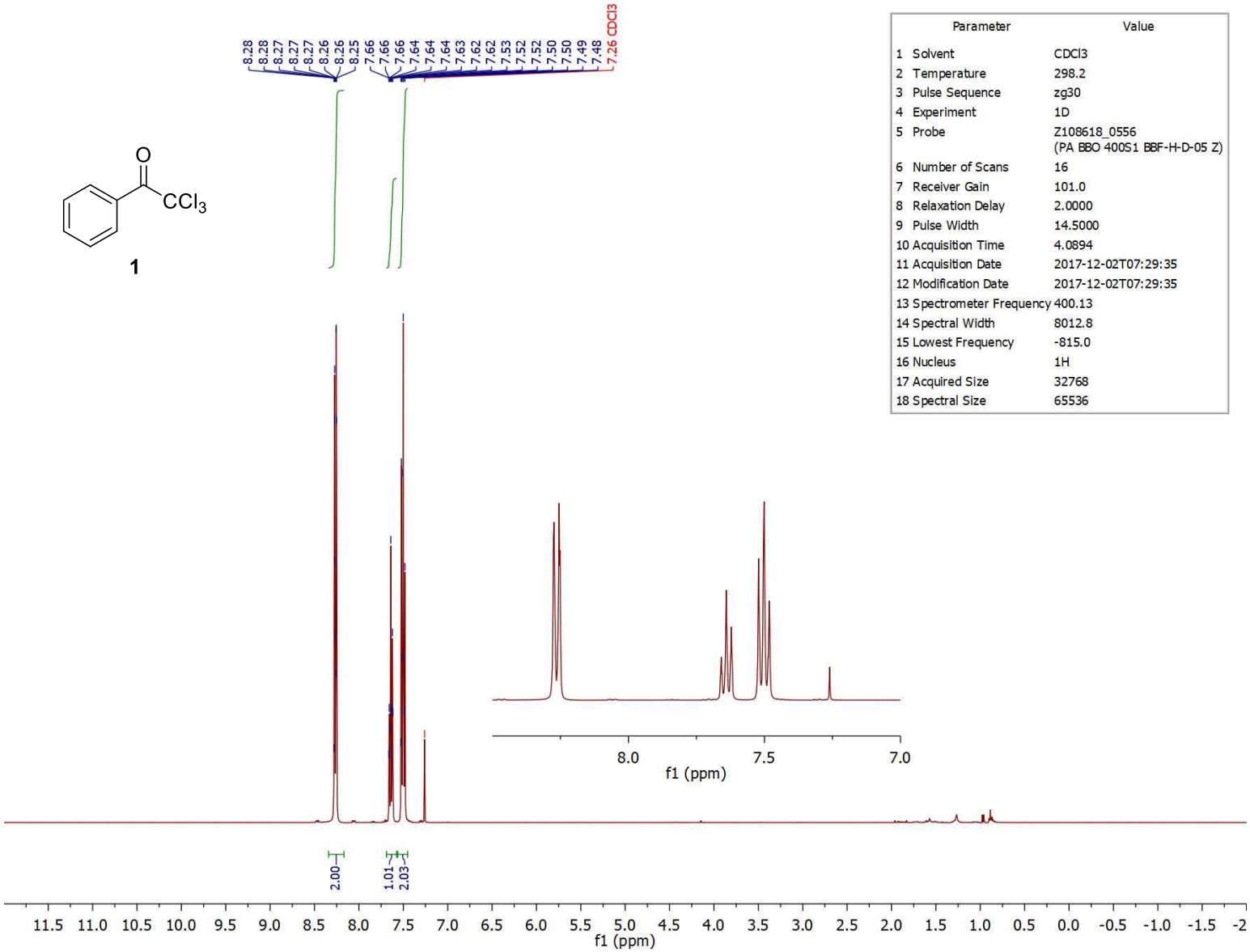
Prof. Hélène Lebel obtained a BSc degree from Université Laval (1993) and a Ph.D. from Université de Montréal (1998). She then joined the group of Eric N. Jacobsen at Harvard University as a NSERC Postdoctoral Fellow. She began her academic career at the Université de Montréal in 1999, under a NSERC University Faculty Award. She was promoted to the rank of Full Professor in 2010. Her research interests focus on the development of new synthetic methodologies in organic chemistry based on transition metal-catalyzed processes.

Henri Piras was born in Paris and raised in l'île de la Réunion, in France. He obtained in 2011, an Engineer degree in synthetic and industrial organic chemistry from the École National Supérieure de Chimie de Clermont-Ferrand, and an MSc degree from Université Blaise-Pascal under the supervision of Prof. Yves Troin. Since January 2012, he has been a Ph.D. student with Prof. Hélène Lebel at Université de Montréal, working on the stereoselective synthesis of chiral sulfilimines and sulfoximines.

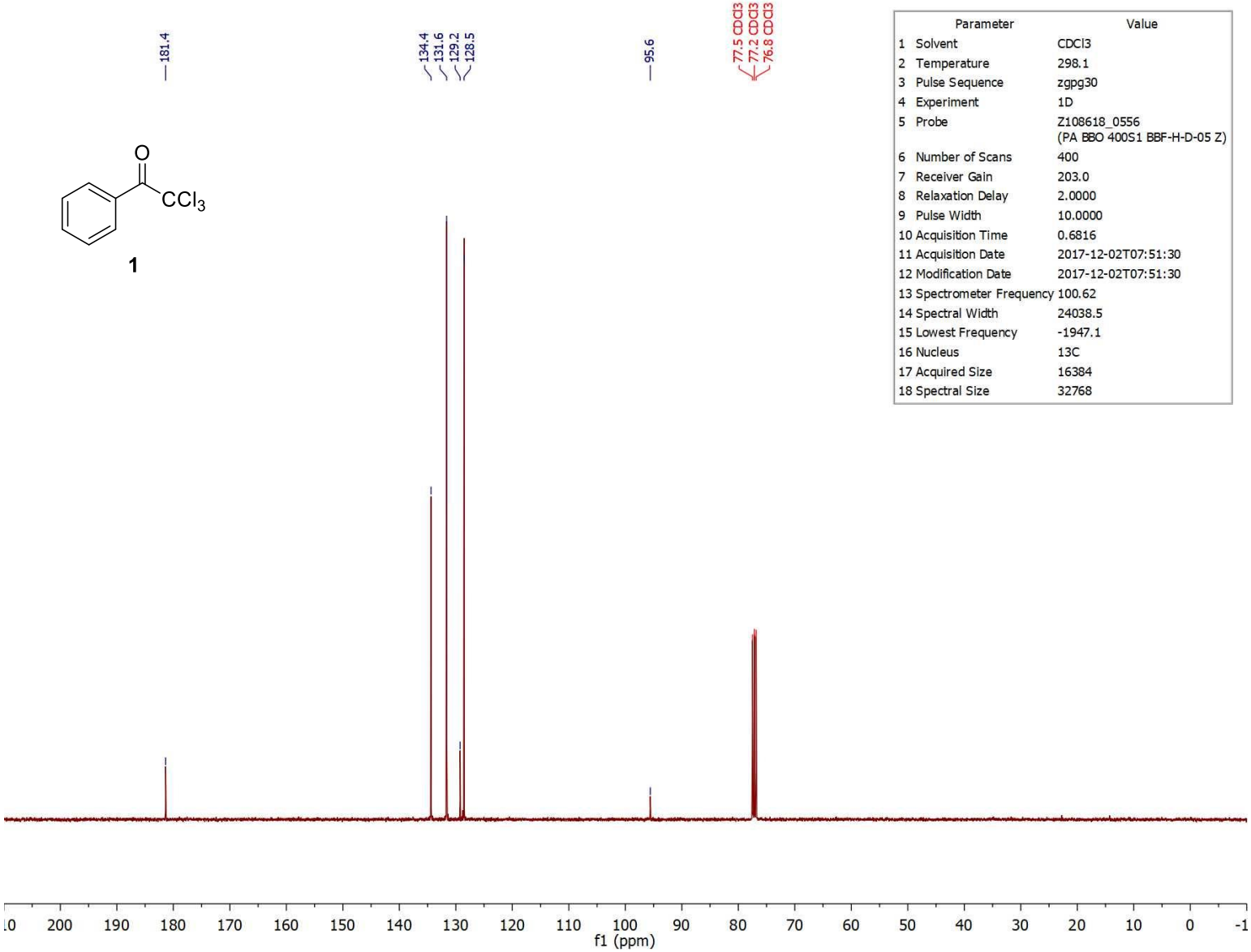
Johan Bartholoméüs was born and raised in Dunkerque, France. He received a Licence de chimie from Université du Littoral Côte d'Opale in Dunkerque in 2007 and a Master 1 in sciences from Université des Sciences et Technologies in Lille in 2008. He then completed a Master 2 in organic synthesis at Université de Bordeaux 1 under the supervision of Prof. Stéphane Quideaux. In September 2011, he joined the group of Prof. Hélène Lebel as a Ph.D. student and is currently writing his thesis on stereoselective amination of C-H bonds to synthesize propargylic amines.

Mario Leypold was born in 1987 in Austria. He studied chemistry at the Graz University of Technology and University of Graz (Austria), and performed his Ph.D. project under the guidance of Professor Rolf Breinbauer. He is currently working as a postdoctoral researcher with an Erwin-Schrödinger-Fellowship in the laboratory of Professor Mohammad Movassaghi (Massachusetts Institute of Technology, USA).

^{1}H NMR (400 MHz, $CDCl_3$) of 2,2,2-Trichloro-1-phenylethane-1-one (**1**)



^{13}C NMR (100 MHz, $CDCl_3$) of 2,2,2-Trichloro-1-phenylethane-1-one (**1**)



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12	Modification Date	2017-12-02T07:51:30
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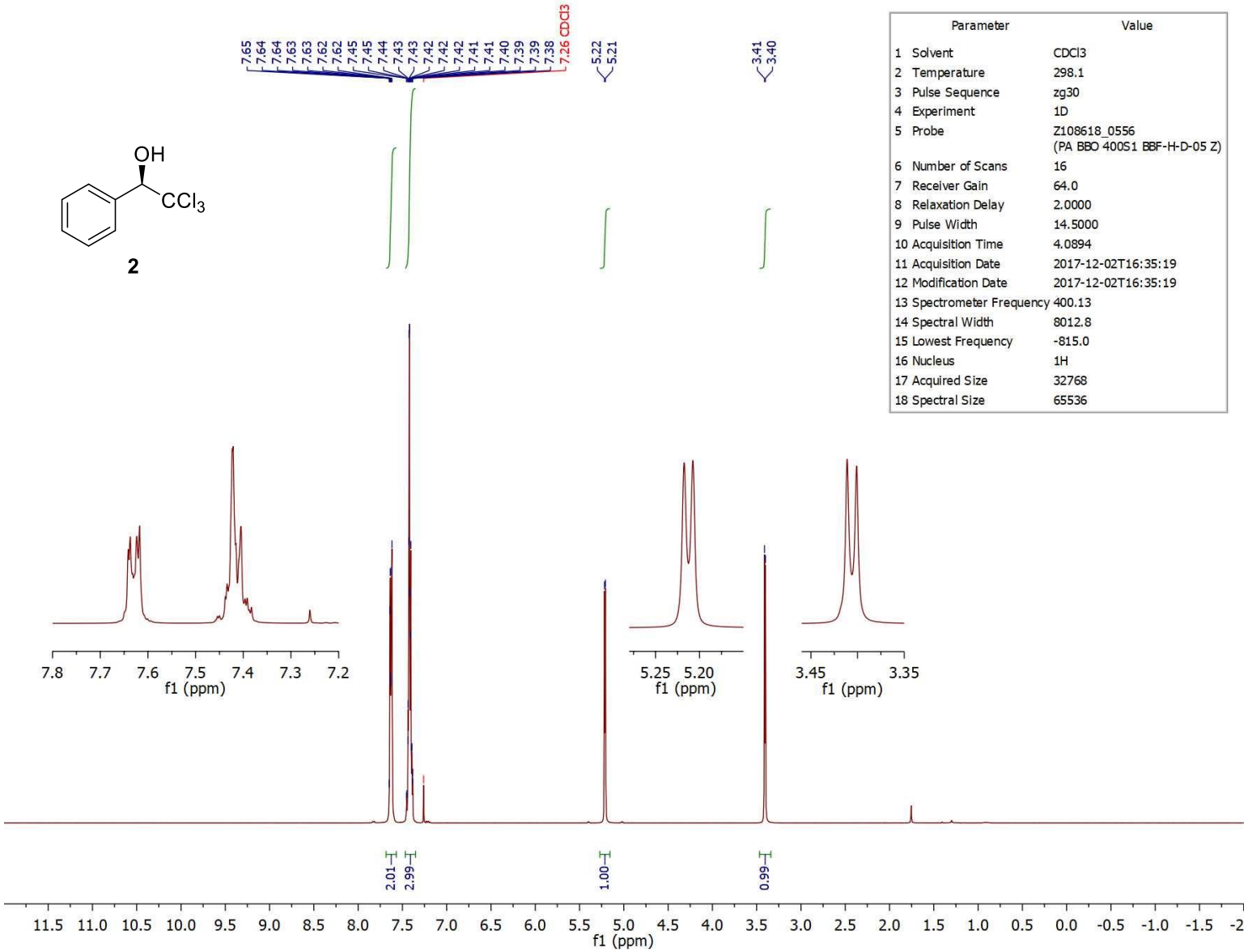
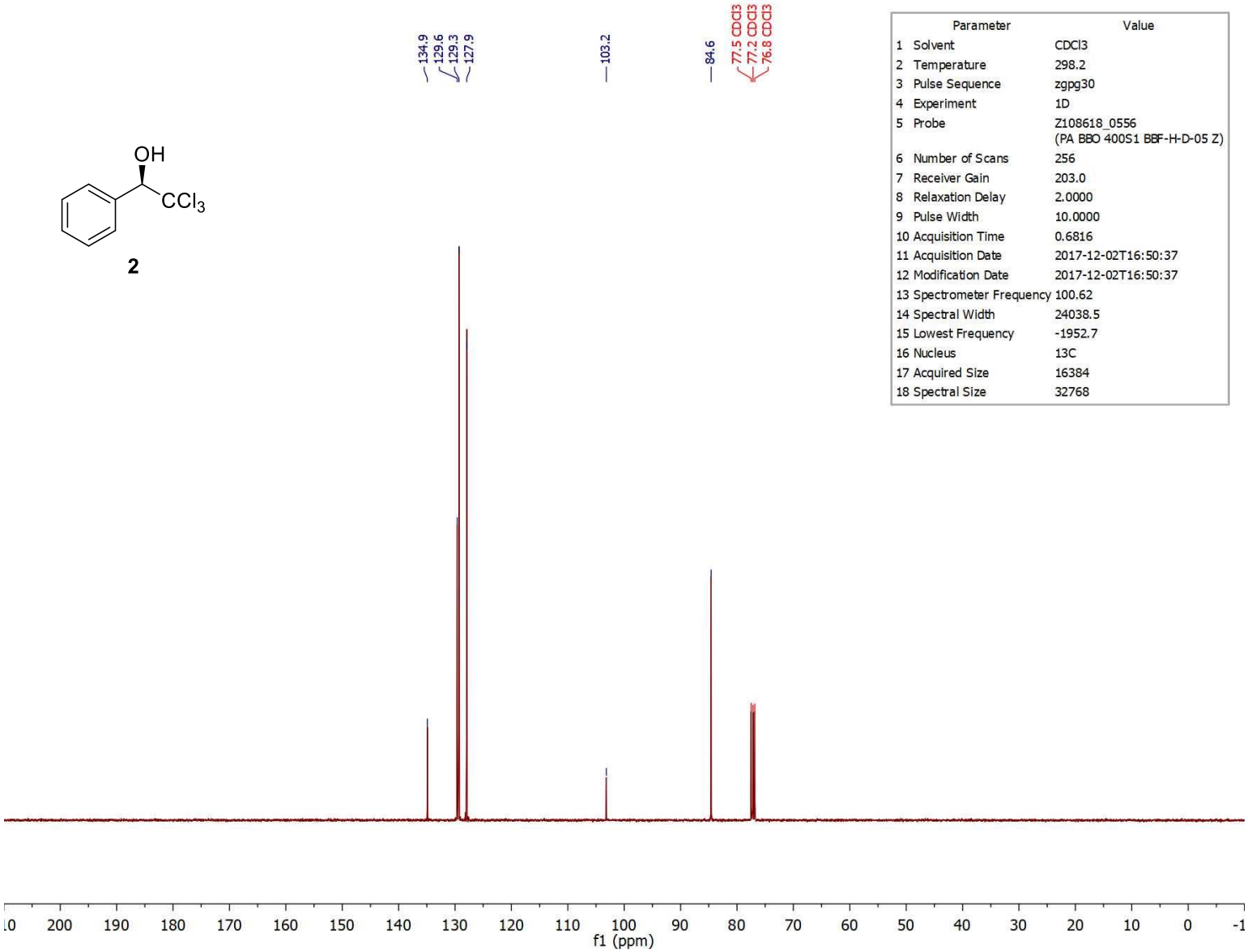
15	Lowest Frequency	-1947.1
16	Nucleus	13C
17	Acquired Size	16384
18	Spectral Size	32768

^{1}H NMR (400 MHz, $CDCl_3$) of (*R*)-2,2,2-Trichloro-1-phenylethane-1-ol (**2**)



^{13}C NMR (100 MHz, $CDCl_3$) of (*R*)-2,2,2-Trichloro-1-phenylethane-1-ol (**2**)



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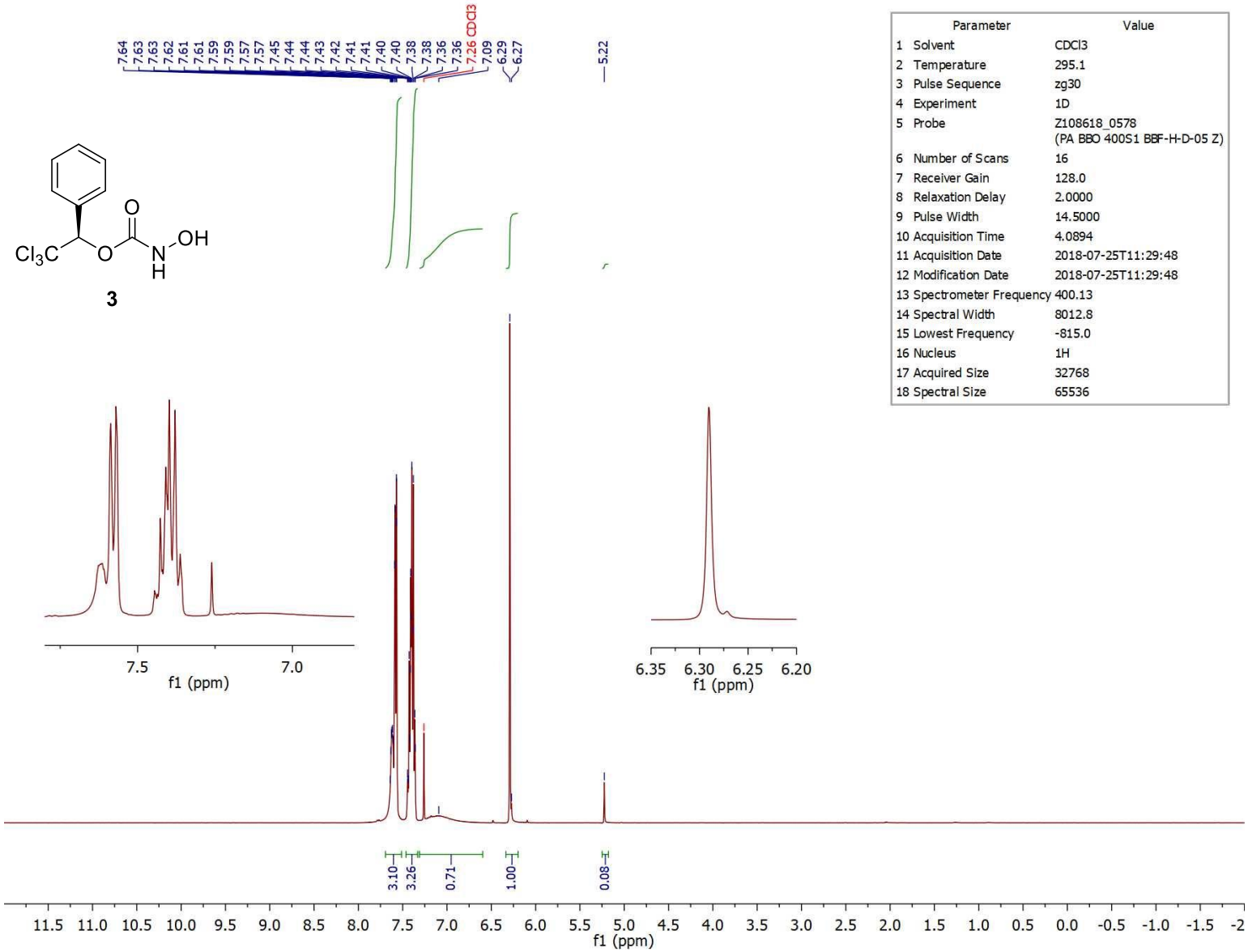
16	Nucleus	13C
17	Acquired Size	16384
18	Spectral Size	32768

^{1}H NMR (400 MHz, $CDCl_3$) of (*R*)-2,2,2-Trichloro-1-phenylethyl hydroxycarbamate (**3**), crude material (92.0% n/n, 93.5% w/w)



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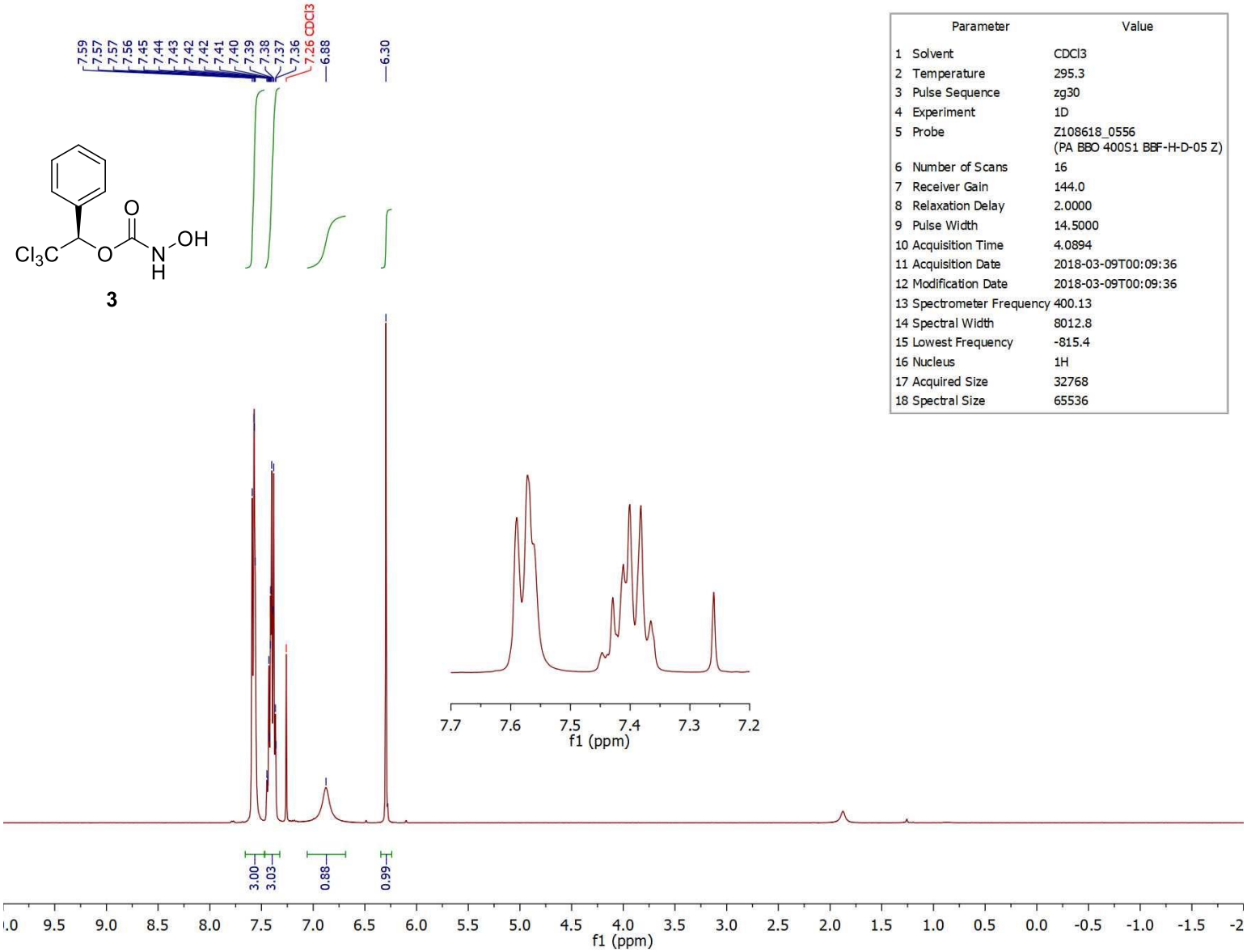
^{1}H NMR (400 MHz, $CDCl_3$) of (*R*)-2,2,2-Trichloro-1-phenylethyl hydroxycarbamate (**3**)



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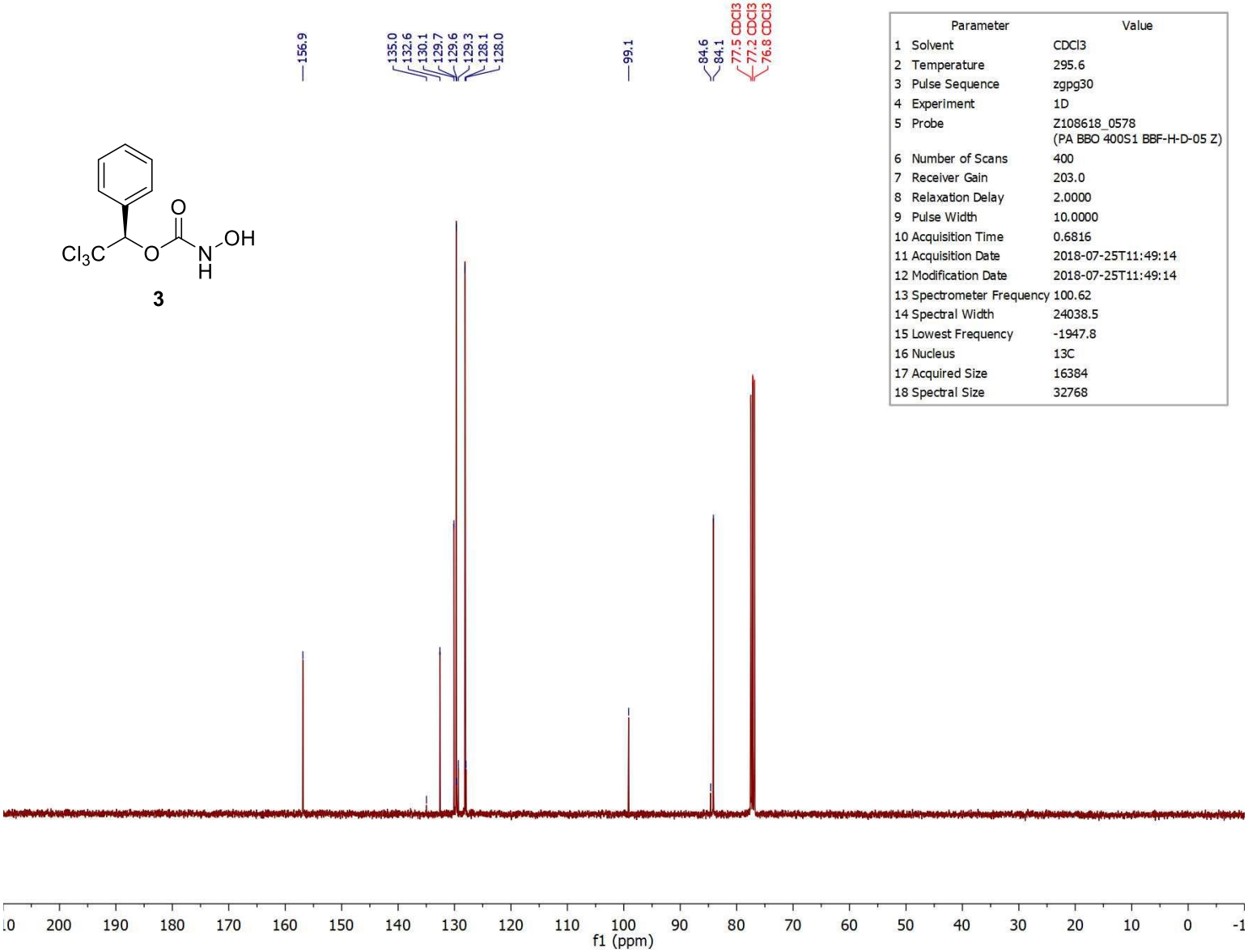
16	Nucleus	1H
17	Acquired Size	32768
18	Spectral Size	65536

^{13}C NMR (100 MHz, $CDCl_3$) of (*R*)-2,2,2-Trichloro-1-phenylethyl hydroxycarbamate (**3**), crude material (92.0% n/n, 93.5% w/w)



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14 Spectral Width	24038.5
15 Lowest Frequency	-1947.8
16 Nucleus	13C
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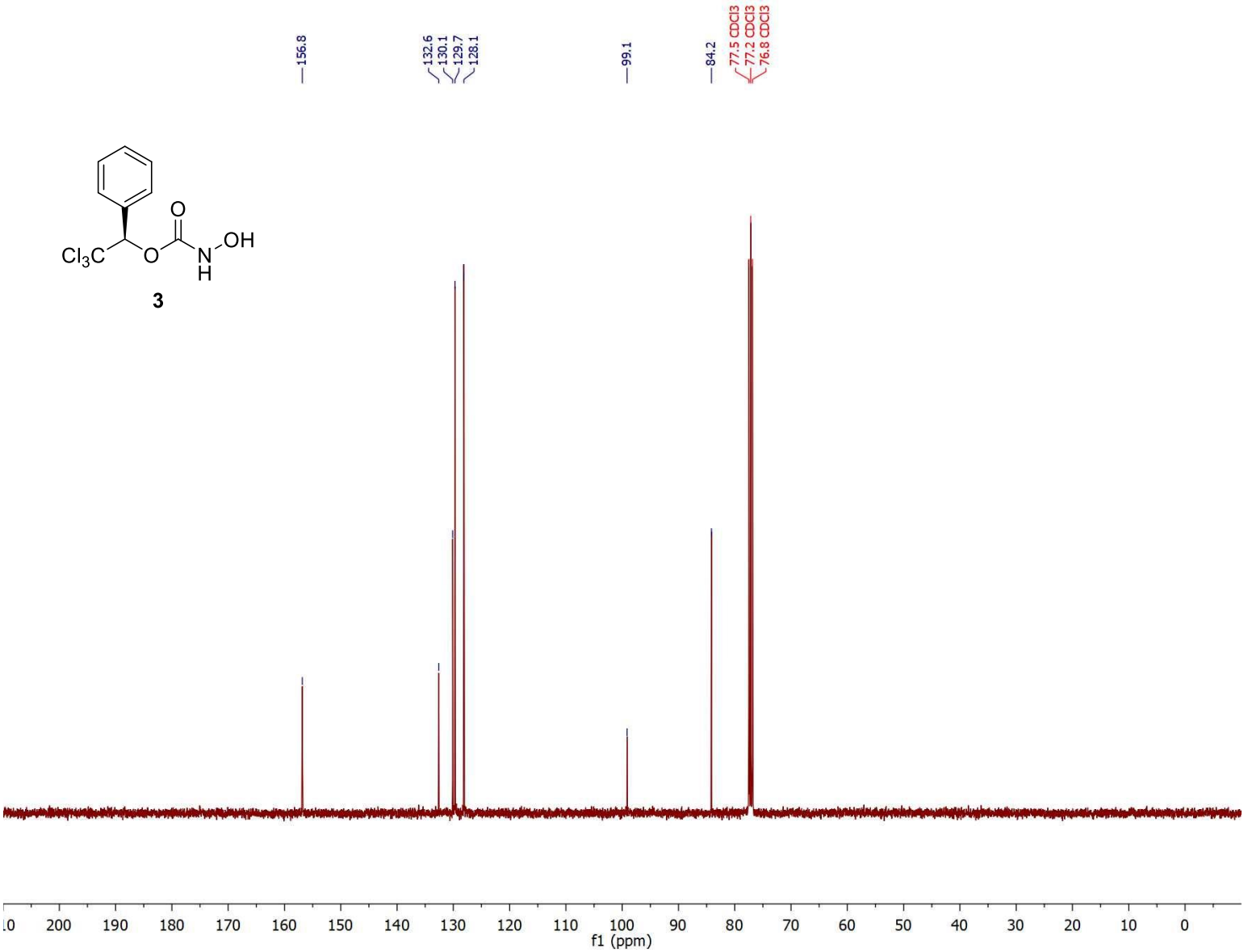
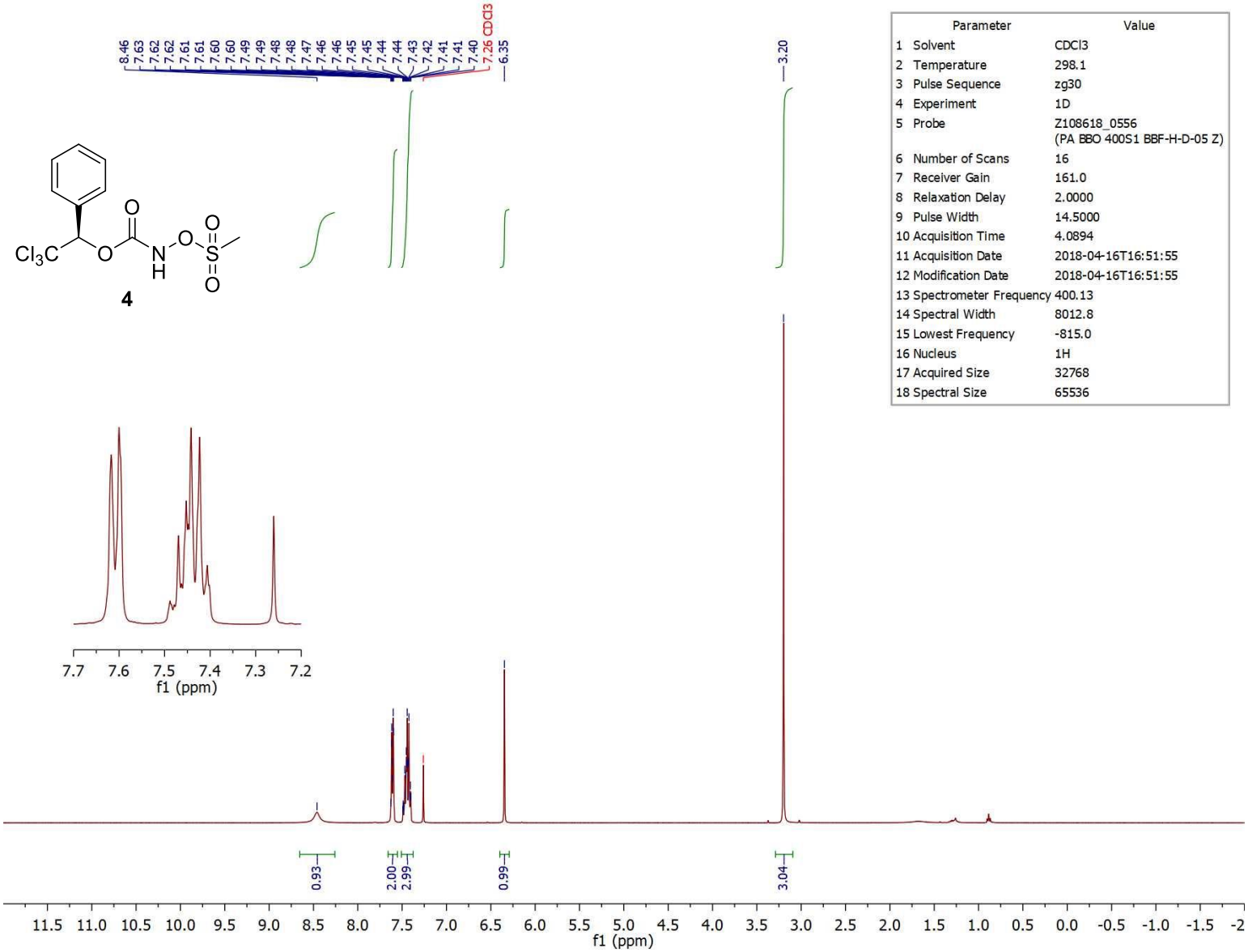
^{13}C NMR (100 MHz, $CDCl_3$) of (*R*)-2,2,2-Trichloro-1-phenylethyl hydroxycarbamate (**3**)



^{1}H NMR (400 MHz, $CDCl_3$) of (*R*)-2,2,2-Trichloro-1-phenylethyl (methylsulfonyl)oxycarbamate (**4**)



^{13}C NMR (100 MHz, $CDCl_3$) of (*R*)-2,2,2-Trichloro-1-phenylethyl (methylsulfonyl)oxycarbamate (**4**)